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To the Editor:

We write to provide comment and perspective on Sewnath and colleagues' recent meta-analysis of the efficacy of preoperative biliary drainage for tumors causing obstructive jaundice.[1] We congratulate the authors on their thorough review and excellent summary of the existing literature. However, we have reservations about the use of meta-analysis of studies on this subject and feel that broader perspectives in the interpretation of the data are needed to guide decisions on preoperative drainage for individual patients.

In this era of evidence-based medicine, the status of randomized prospective trials has been elevated. This is usually justified. However, not all randomized trials are created equal. Older clinical research was conducted during an era when there was considerably less rigor in design, interpretation, and reporting of randomized clinical trials. Including such trials in a meta-analysis can significantly impact the estimates of the efficacy of an intervention.[2] The basic principles of clinical trial reporting embodied in the Consolidated Standards of Reporting Trials (CONSORT) statement[3,4] were not uniformly followed before the mid 1990s, leading to significant methodologic and reporting deficiencies in older randomized trials.[5] The five randomized trials reviewed by Sewnath et al. were poorly designed with broad eligibility criteria (including both proximal and distal tumors), small sample sizes, nonexistent (three trials) or suboptimal (one trial) biostatistical designs, various interventions (internal or external biliary drainage), and various surgical procedures. These trials reflect 1970s approaches to biliary obstruction and surgery, with high usage of external biliary drains (59%), low resection rates (16%), and significant rates of perioperative death (12%). As such, the treatment in the level 1 studies bears little resemblance to current approaches to malignant biliary obstruction. Indeed, no statistical methodology can make up for fundamental deficiencies in individual trial design, wide variations in eligibility criteria, nonexistent biostatistical design, and outdated therapeutic approaches. Thus, it is impossible for meta-analysis, as a statistical method, to draw meaningful conclusions from these trials, and the interpretation of the aggregate level 1 evidence evaluating complications associated with preoperative biliary drainage is restricted.

There are additional issues that make interpretation of the level 2 evidence problematic as well. In addition to the nonrandomized nature of the comparisons, the retrospective data on preoperative biliary stenting tend to be biased. As demonstrated by statistical analysis in our recent report,[6] patients who undergo preoperative endobiliary stent placement are typically older with more extensive co-morbid conditions, including relative malnutrition. In addition, the exceedingly important variable of performance status is not usually quantified in retrospective reports but is certainly a factor in clinical decision-making. Any comparison of outcome in stented versus unstented patients is therefore prone to bias.

The results of the meta-analysis must also be viewed in the context of how patients are treated. The majority of patients with obstructive jaundice of extrahepatic etiology present to a primary care physician and are referred directly to a gastroenterologist. Surgeons are often out of the decision-making loop regarding prereferral diagnostic procedures, cholangiography, and placement of an endobiliary stent. Moreover, very few surgeons have the capacity to schedule timely definitive surgery for patients who present with malignant biliary obstructions and require preoperative assessment of co-morbidity and planning of elective, major surgical procedures. Therefore, as a practical matter, many patients with symptomatic jaundice require pretreatment biliary decompression.

Of greater concern in the direct extrapolation of the meta-analysis results is the known relationship between the institutional volume of major oncologic surgery and the resulting morbidity and mortality rates. As recently outlined by Birkmeyer and colleagues in an analysis of 2.5 million complex surgical procedures, over 50% of Medicare patients in the United States undergo pancreaticoduodenectomy at institutions that perform relatively low volumes of this procedure, and the associated mortality rates exceed 10%.[7] Therefore, physicians should be cautious in drawing inferences about the timing of surgery from the meta-analysis. Immediate surgery may be the best option only for the minority of patients who present with jaundice to high-volume centers. The safest overall public health policy for the management of patients with malignant biliary obstruction may be to proceed with nonoperative relief of jaundice by endobiliary stent placement. Following biliary decompression, the patient should be considered for referral to a regional center for more definitive staging and determination of therapeutic options. A public health policy of "stent placement and referral" will likely result in significant overall cost savings and reduction in treatment-related morbidity and mortality rates for patients with obstructive jaundice.

Certainly, reasonable recommendations for individual patient management that can be drawn from the existing literature would include:

1. Whenever possible, an experienced pancreaticobiliary surgeon should be involved in the decision-making regarding pretreatment cholangiography and biliary stent placement for patients who present with obstructive jaundice, and;
2. Whenever option 1 is not possible (regrettably, in the majority of patients), a policy of endobiliary stent placement and tertiary-care referral is reasonable.

While it is fashionable to advocate design and implementation of a "definitive randomized trial," the reality is that a clinical trial restricted to patients with proximal or lower biliary tract obstruction could never be completed for practical and logistical reasons. To our knowledge, no such trials have been initiated since 1988. Given the significant limitations of the level 1 evidence, the existing body of retrospective cohort data with larger patient populations treated with modern endoscopic endobiliary drainage and undergoing similar surgical procedures assumes increased importance. Thus, this may be a situation in which homogeneous retrospective cohort analysis may provide better clinical guidance than caveat-laden meta-analysis of a limited group of heterogeneous, older-generation, small randomized controlled trials performed in patients who predominantly underwent external biliary drainage.

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Author's Reply:

We thank Dr. Pisters et al. for their interest, critical comments, and important remarks about our recent meta-analysis published in *Annals of Surgery*.[1] The comments can be separated into four different parts that will be discussed accordingly.

1. Reservation about the use of meta-analysis.

We fully agree that the interpretation of a meta-analysis should be done with caution. It might provide the highest level of evidence if the inclusion of trials is according to the critical criteria of the CONSORT[2] statement. Unfortunately many recently published meta-analyses, as ours, also included data of studies with substantial methodologic deficiencies. It can be discussed if these meta-analyses should be performed and if journals should accept these studies with inevitable shortcomings for publication. The advantage of performing these analyses is however, that it still provides the best insight in the available clinical data (including shortcomings) and the statistics are used to evaluate the overall effect. Interpretation of these findings should be critical and is even more important. The flaws of the randomized trials, as well as level 2 studies included in our meta-analysis are nicely summarized by Pisters et al., have also been discussed in our paper.

2. The outcome of the meta-analysis.

Despite the shortcomings of many studies included in the meta-analysis there seems not to be a strong disagreement between Pisters et al. and the authors concerning the outcome of the studies. There is agreement that there is limited difference in mortality and morbidity (except for a slight increase of infections) of patients undergoing surgery with or without preoperative biliary drainage.

3. Interpretation of findings of the meta-analysis

Disagreement exists however about the interpretation of the data from this study. We concluded that preoperative biliary drainage should not be performed routinely. When additional, invasive, expensive procedure does not reduce the morbidity of subsequent surgery and do not improve outcome, but still increases hospital stay this procedure should not performed routinely. We still prefer first to aim at "medical evidence" of the procedure/strategy and subsequently try to improve logistics accordingly or if this proved to be impossible accept second best.

Pisters et al. concluded that drainage does not harm and therefore should be performed to create length of time to consider referral of patients to centers. The important message behind this strategy is the known correlation of hospital volume and mortality after surgery.[3] A correlation of hospital volume and mortality for pancreaticoduodenectomy is found in the Netherlands.[4] However it is known that there is also a hospital volume-outcome effect for ERCP and stenting. Even in our institution with a high case-load and experience in endoscopic drainage procedures stent replacement and cholangitis was found in 30%.[5] A limited morbidity of endoscopic stent placement in general practice cannot be expected, however this aspect is not mentioned by Pisters et al. Therefore we still prefer early referral without any intervention, immediately after CT scan staging shows a potential resectable lesion without metastases. Interpretation of these CT scans by experts can easily be performed by e-mail nowadays. This is also an inclusion criteria of our next trial. Indeed we agree that there is an advantage to perform surgery in high volume centers but following this strategy this might be possible without preoperative biliary drainage.

There also seems to be a remarkable difference of strategy in the US where in the Eastern part of the country early surgery without drainage is generally preferred and strongly advocated whereas in the South part this seems not to be possible.[6–9]

4. The discussion of general acceptance of ERCP and drainage as an routine peroperative procedure as proposed by Pisters et al. is important for future trials

If preoperative chemo- and radiotherapy are effective in phase II studies, a randomized trial will generally follow soon to further evaluate/prove the efficacy of this treatment. In the concept of Pisters et al. these patients probably will be randomized after adequate endoscopic drainage and extensive staging (diagnostic laparoscopy, etc.). An argument might be that drainage is indicated before chemotherapy can be started. Generally, this concept, at least in the Netherlands, will take about 4–8 weeks. This strategy could be a disadvantage for patients without chemotherapy. Others in favor of early surgery should prefer randomization immediately after staging CT scan and compare early surgery (and resection) versus delayed surgery after drainage, chemotherapy, and resection. These different strategies might influence the outcome of that study.

Considering the above-mentioned arguments, we still prefer a well designed randomized trial over of a retrospective cohort analysis to obtain clinical guidance in the issue of preoperative drainage. However, we also do realize the potential impact of that trial on logistics and changes of referral patterns. In the August 2002 issue of *Gastrointestinal Endoscopy*, a retrospective study on preoperative decompression of Pisters et al., as well as a study

from our institution (Sewnath et al.) were reviewed by Dr Isenberg. He concluded that the conflicting data, in particular the recent noticed increase of infectious complications after drainage, reinforced the need for a prospective trial and suggested that the National Institute of Health should facilitate and fund such a study.[10,5,6] A comment of Dr Pisters and one of the authors was included. In that comment it was mentioned already that we will start such a trial in the Netherlands soon and do realize it might be difficult to conduct because of referral pattern, other logistics as diagnostic procedures, waiting lists, preoperative stagings, etc. It was also mentioned that diagnostics in the United States and referral to centers might be more difficult for implementation of an early surgery strategy. So Dr. Pisters' message was already well taken previously.

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